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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
LUCA RAMPOLDI, ET AL.	: EXAMINER: GEORGE
SERIAL NO: 10/615,781	:
FILED: JULY 10, 2003	: GROUP ART UNIT: 1616
FOR: PHARMACEUTICAL COMPOSITIONS WITH ANTIBIOTIC ACTIVITY	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This brief is submitted in response to the rejections dated April 6, 2006.

REAL PARTY OF INTEREST

The real party of interest herein is Zambon, S.p.A., Milan, Italy.

RELATED APPEALS AND INTERFERENCES

None

STATUS OF CLAIMS

Claims 9-23 are active in this application.

Claims 9-23 are rejected and appealed.

STATUS OF AMENDMENTS

An Amendment to the claims was filed after a final rejection on June 30, 2006. The Advisory Action of September 14, 2006 indicated the amendments would be entered for purposes of this Appeal. Therefore, in the attached Claim Appendix I, the claims are presented in the amended form.

SUMMARY OF CLAIMED SUBJECT MATTER

As set forth in independent Claim 9, the invention currently under examination is

A process for stabilizing a Fosfomycin Tromethamol composition, the process comprising: ***(disclosed in the specification on page 1, lines 4-8)***

combining Fosfomycin Tromethamol with at least one of the following substances in an amount effective to stabilize the Fosfomycin Tromethamol: ***(disclosed in the specification on page 1, lines 17-19; and page 2, line 2)***

a tribasic sodium citrate; a tribasic potassium citrate; a monoacidic sodium citrate; a monoacidic potassium citrate; a tribasic sodium phosphate; a tribasic potassium phosphate; a monoacidic sodium phosphate; a monoacidic potassium phosphate; a sodium carbonate; a potassium carbonate; a sodium bicarbonate; a potassium bicarbonate; a sodium tartrate; a potassium tartrate; an arginine; and a lysine.***(disclosed in the specification on page 1, line 22 through page 2, line 2)***

The invention also relates to a pharmaceutical composition (Claim 17) combining Fosfomycin Tromethamol and at least one of the substances listed above ***(described in the specification on page 2, lines 4-15)***

GROUNDS TO BE REVIEWED ON APPEAL

The sole ground to be reviewed on appeal is the rejection Claims9-23 under 35 U.S.C. § 103(a) as being allegedly unpatentable in view of the combination of U.S. patent publication 2003/0078215 ("Shastri") in view of RxListMonographs (2002).

ARGUMENTS

In rejecting a claim under 35 U.S.C. § 103(a), the USPTO must support its rejection by "substantial evidence" within the record,[1] and by "clear and particular" evidence[2] of a suggestion, teaching, or motivation to combine the teachings of different references. As discussed above, there is no substantial evidence, nor clear and particular evidence, within the record that teaches all of the limitations of the pending claims. Without such suggestion or teaching and absent improper hindsight reconstruction,[3] the pending claims are believed to be non-obvious and patentable over the applied references.

The claimed invention of stabilizing Fosfomoycin Tromethamol with certain substances and stabilized pharmaceutical compositions containing the same. The primary piece of art cited in the rejection, Shastri, describes embedded within a laundry list of various antibiotics--a different material Fosfomycin. Shastri also suggests that is possible to include other conventional additives. The secondary reference relied upon in the rejection, RxList Monographs teaches Fosfomycin Tromethamine. There is insufficient teachings in the combination of these references so that one would know how to stabilize Fosfomycin Tromethamol with the particular stabilizing agents being claimed.

As discussed in the specification on page 1, fosfomycin tromethamol has instability problems caused by reactive functional groups and as such degrades. It should be recognized then that this instability leads to significant problems with storing the raw material, preparing

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[1] In re Gartside, 203 F3d 1305, 53 USPQ2d 1769 (Fed. Cir. 2000) (holding that, consistent with the Administrative Procedure Act at 5 USC 706(e), the CAFC reviews the Board's decisions based on factfindings, such as 35 U.S.C. § 103(a) rejections, using the 'substantial evidence' standard because these decisions are confined to the factual record compiled by the Board.)

[2] In re Dembiczak, 175 F3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("We have noted that evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved, although 'the suggestion more often comes from the teachings of the pertinent references.' The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular.") (emphasis added).

[3] See MPEP 2141, stating, as one of the tenets of patent law applying to 35 USC 103, that "[t]he references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention."

compositions with the material, and storing the completed packages. In fact, as stated in the specification on page 1, line 12, the stability issues that have been encountered with the Fosfomycin tromethamol means that as of the filing of the application, the pharmaceutical preparations that are available are in the form of hydrosoluble granules. The Inventors' discovery that certain substances (as defined in the specification and claims) stabilize fosfomycin tromethamol significantly advances the state of this field, permitting the possibility of actually using this material as an antibiotic.

Shastri discloses a composition comprising a fosfomycin as an antibiotic amongst many and some conventional agents. However, Shastri does not disclose the claimed combination of a fosfomycin tromethamol and the stabilizing agents. Fosfomycin tromethamol and fosfomycin are distinct compounds. (See Barry et al., Antimicrobial Agents and Chemotherapy, June 1991, p. 1235-1238, made of record on November 17, 2005). According to Barry, "fosfomycin tromethamine [is](previously fosfomycin tromethamol)" (see page 1235, second sentence of the second paragraph), and "fosfomycin tromethamol dissociates into two molecules, fosfomycin (molecular weight, 138) and tromethamine (molecular weight, 121)" (see page 1235, first sentence of the third paragraph). The RxList is relied on to allege that certain dosage amount of fosfomycin tromethamine is taught (see page 6 of the Office Action), and to conclude that the combined teachings of Shastri and the RxList result in the claimed invention. Applicants' disagree.

First, as Shastri describes fosfomycin and the RxList describes fosfomycin tromethamol, the teachings applicable to each chemically distinct compound are not simply combinable. Second, even if one assumed that the dosage amount in the RxList would be applicable to the Shastri's composition, since Shastri describes a different compound than the one recited in the claims, the combination of Shastri and the RxList does not render the claimed invention obvious.

Even more fundamentally it should be noted that Shastri's disclosure is not directed to stabilizing even the Fosfomycin described therein. Rather, Shastri's "invention" is to increase activity of bioactive agents, such as antibiotics generally, with a complexing agent, such as cyclodextrin (see page 1, [0003]). Indeed, in discussing the bioactive agents as antibiotics, Shastri envisions any and all possible antibiotics benefiting from this complex (see page 2, [0021]) and, in fact, only show data for cyclodextrin (see [0010]).

Shastri does not even remotely suggests the necessity of stabilizing Fosfomycin Tromethamol nor that one could address this problem with a select number of stabilizing agents as defined in the claims. The RxList Monographs states nothing other than a description of a known pharmaceutical, the very one described on page 1 of the present application that has serious deficiencies in terms of stability. How is it that one following the teachings of Shastri, one would have sought to include one or more of the specific agents with an expectation that it would have stabilized the drug? There is none because Shastri only in passing mentions Fosfomycin as a potential candidate for its complex and suggest optional excipients including sodium bicarbonate (see [0082]).

Notwithstanding the clear differences, the rejection has been maintained rejection because "it is the position of the Examiner that the bioactive agents of the prior art as recited are directed toward the broad disclosure of the activation. One of ordinary skill in the art of drug preparation would have the understanding of preparing that active agent with a salt, if the salt of the drug would better suit the preparation."(page 3 of the Official Action of April 6, 2006). However, this conclusion misses a fundamental point of difference, which is that the present invention is based on the discovery that certain agents can stabilize fosfomycin tromethamol (Claim 9 is directed to a method of stabilizing and Claim 17 is directed to a composition in which the agent is present in an amount effective for stabilizing). There is

simply no description, teaching or otherwise any suggestion in the cited documents for the problems of stabilizing fosfomycin tromethamol or how one would go about solving this problem. Therefore, regardless of whether one would have an understanding that salts would be more useful (as alleged by the Office), there is no description for the invention as claimed.

In summary, there is simply nothing in the cited art relied upon in the rejection to establish that it would have been obvious to specifically combine Fosfomycin Tromethamol with the specific agents listed in the claims with the expectation that these agents as opposed to any of the number of possible excipients described by the art would, in fact, stabilize as has been found by the Inventors of the present application.

Therefore, it is respectfully submitted that the prior art cited in the rejection does not render the claimed invention obvious.

Reversal of this rejection is requested.

A Notice of Allowance for pending claims 9-23 is also requested.

Respectfully submitted,

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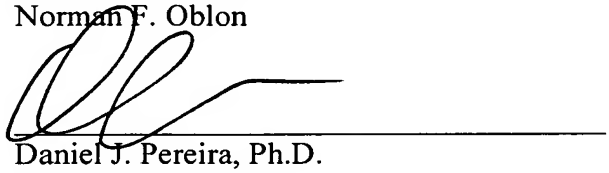

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APPENDIX 1 (CLAIMS)

Claims 1-8 (Canceled)

9. (Previously Presented) A process for stabilizing a Fosfomycin Tromethamol composition, the process comprising:

combining Fosfomycin Tromethamol with at least one of the following substances in an amount effective to stabilize the Fosfomycin Tromethamol:

a tribasic sodium citrate;

a tribasic potassium citrate;

a monoacidic sodium citrate;

a monoacidic potassium citrate;

a tribasic sodium phosphate;

a tribasic potassium phosphate;

a monoacidic sodium phosphate;

a monoacidic potassium phosphate;

a sodium carbonate;

a potassium carbonate;

a sodium bicarbonate;

a potassium bicarbonate;

a sodium tartrate;

a potassium tartrate;

an arginine; and

a lysine.

10. (Previously Presented) The process of claim 9, wherein the stabilizing substance is one or more of: a tribasic sodium citrate, a sodium carbonate, a potassium carbonate, a sodium bicarbonate, a potassium bicarbonate, and an arginine.

11. (Previously Presented) The process of claim 9, wherein a molar ratio of the substance with respect to Fosfomycin Tromethamol is in a range between 10% and 100%.

12. (Previously Presented) The process of claim 9, wherein a molar ratio of the substance with respect to Fosfomycin Tromethamol is in a range between 30% and 70%.

13. (Previously Presented) The process of claim 9, wherein a molar ratio of the substance with respect to Fosfomycin Tromethamol is at least 50%.

14. (Previously Presented) The process of claim 9, wherein the Fosfomycin Tromethamol and the stabilizing agent are produced as a hydrosoluble granulate.

15. (Previously Presented) The process of claim 9, wherein the Fosfomycin Tromethamol is present in the composition in an amount of approximately 5.6 g.

16. (Previously Presented) The process of claim 9, further comprising adding an excipient agent.

17. (Previously Presented) A pharmaceutical composition comprising Fosfomycin Tromethamol and at least one substance, in an amount effective for stabilizing, selected from the group consisting of:

a tribasic sodium citrate;

a tribasic potassium citrate;

a monoacidic sodium citrate;

a monoacidic potassium citrate;

a tribasic sodium phosphate;

a tribasic potassium phosphate;

a monoacidic sodium phosphate;

a monoacidic potassium phosphate;

a sodium carbonate;

a potassium carbonate;

a sodium bicarbonate;

a potassium bicarbonate;

a sodium tartrate;

a potassium tartrate;

an arginine; and

a lysine.

18. (Previously Presented) The pharmaceutical composition of claim 17, wherein the stabilizing substance is one or more of: a tribasic sodium citrate, a sodium carbonate, a potassium carbonate, a sodium bicarbonate, a potassium bicarbonate, and an arginine.

19. (Previously Presented) The pharmaceutical composition of claim 17, wherein a molar ratio of the substance with respect to Fosfomycin Tromethamol is in a range between 10% and 100%.

20. (Previously Presented) The pharmaceutical composition of claim 17, wherein a molar ratio of the substance with respect to Fosfomycin Tromethamol is in a range between 30% and 70%.

21. (Previously Presented) The pharmaceutical composition of claim 17, wherein a molar ratio of the substance with respect to Fosfomycin Tromethamol is at least 50%.

22. (Previously Presented) The pharmaceutical composition of claim 17, wherein the Fosfomycin Tromethamol is present in an amount of approximately 5.6 g.

23. (Previously Presented) The pharmaceutical composition of claim 17, which is produced as a hydrosoluble granulate.

APPENDIX II (EVIDENCE)

Barry et al., Antimicrobial Agents and Chemotherapy, June 1991, p. 1235-1238 filed in the record on November 17, 2005

RELATED PROCEEDINGS APPENDIX

None.